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Methylene acetals as protecting groups - an improved preparation method

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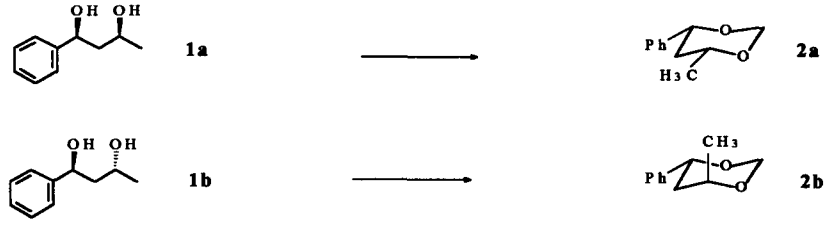
Abstract. A facile method to protect *vic* diols, 1,3 diols and other hydroxyl functions as methylene acetals is achieved by treating the relative substrates with $POCl_3$ or $SOCl_2$ in DMSO. The good yields obtained, the good solubility of many organic compounds in DMSO and the easy hydrolysis of the 1,3,5-trioxaepane derivatives prepared from *trans vic* diols make useful this protecting method. © 1997 Published by Elsevier Science Ltd.

The methylene acetals are widely used as protection of diolic functions. To avoid the not always suitable classical reaction with CH_2O in protic acid conditions, it has been reported the preparation of methylene acetals with CH_2Br_2/KOH in DMSO [1] or with DMSO in organic solvents in the presence of a catalyst as NBS [2], PPA [3], ($CH_3)_3SiCl$ [4], or Br_2 [5]. Some of these reactions need drastic conditions, others could cause side reactions if the substrates contained functional groups interacting with the catalyst. We here report an improved method which employs DMSO as source of methylene in the presence of $POCl_3$ or $SOCl_2$ as catalyst, requires mild conditions, short reaction time and generally does not cause side reactions.
This new methodology has been checked on four groups of compounds: acyclic diols, cyclic diols, carbohydrates and also monovalent alcohols from which intermolecular acetals has been obtained (see table 1). Finally it was checked the stability of dioxolane, dioxane, and trioxaepane cycles obtained towards acid hydrolytic condition

Group 1: 1,3-Aliphatic acyclic diols.
We submitted to this reaction the *eritro* (**1a**) and *threo* (**1b**) 1-phenyl-1,3-butane-diols. Both compounds were transformed with high yields into the corresponding 6-methyl-4-phenyl-1,3-dioxanes (**2a** and **2b**). To test the selectivity of this reaction, we used as substrates also a complex natural compound as rifamycin S [6] which showed a 1,3-diol function in its ansa-chain and many different functions in its molecule. We obtained with high yield the expected 1,3-dioxane derivative. No modifications were found in the other functions.

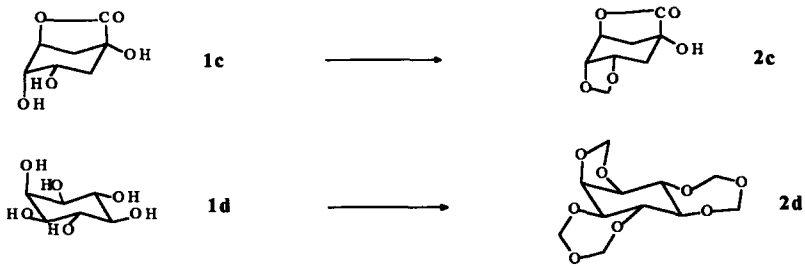


Product	Yield (%) $t_{reac.}$ (min) $POCl_3$	Yield (%) $t_{reac.}$ (min) $SOCl_2$	$[\alpha]_D$ (c, solv.)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$) δ (ppm)
2a	95 30	95 30	-20 ± 2.1 (1.1, CHCl3)	$C_{11}H_{14}O_2$ (178.23)	**1.36** (d, 3H, J=6.6 Hz, CH_3) **1.87** (ddd, 1H, J=4.3, 6.1, 13.7 Hz, H-5ax) **2.25** (ddd, 1H, J=4.2, 6.8, 13.7 Hz, H-5eq) **4.10** (ddq, 1H, J=4.2, 6.1, 6.6 Hz, H-6ax) **4.69** (d, 1H, J=6.6 Hz, -OCH_2O-) **5.00** (dd, 1H, J=4.3, 6.8 Hz, H-4ax) **5.03** (d, 1H, J=6.6 Hz, -OCH_2O-) **7.30** (m, 5H, -phenyl).
2b	90 30	85 30	1.5 ± 1.3 (1.2, CHCl3)	$C_{11}H_{14}O_2$ (178.23)	**1.27** (d, 3H, J=6.2 Hz, CH_3) **1.71** (m, 2H, H-5ax , H-5eq) **3.86** (m, 1H, H-6eq) **4.59** (dd,1H, J=2.7, 11.3 Hz, H-4ax) **4.90** (d, 1H, J=6.4 Hz, -OCH_2O-) **5.23** (d, 1H, J=6.4 Hz, OCH_2O-) **7.34** (m, 5H, -phenyl).
2c	88 120		-42.5 ± 1.2 (1.2, CHCl3)=	$C_9H_9O_5$ (185.04)	**2.17** (dd, 1H, J=3.4, 14.7 Hz, H-6ax) **2.30** (m, 1H, H-2ax) **2.40** (ddd, 1H, J=2.4, 7.8, 14.7 Hz, H-6eq) **2.56** (d, 1H, J=11.9 Hz, H-2eq) **3.13** (s, 1H, -OH-1) **4.15** (m, 1H, H-4eq) **4.32** (m, 1H, H-5ax) **4.75**(m, 1H, H-3eq) **4.78** (s, 1H, -OCH_2(exo)O-) **5.19** (s, 1H, -OCH_2(endo)O-).
2d	92 30			$C_{11}H_{16}O_5$ (276.08)	**3.46** (mc, 1H, H-5ax) **3.50** (mc, 1H, H-4ax) **3.77** (dd, 1H, J=3.5, 9.1 Hz, H-1ax) **3.90** (mc, 1H, H-6ax) **4.17** (mc, 1H, H-3ax) **4.20** (mc, 1H, H-2eq) **4.86-5.09** (9H,-OCH_2O-) **5.20** (s, 1H, -OCH_2(endo)O-).
2e	92 30	83 30	246.5 ± 6.9 (0.5, $CHCl_3$)	$C_{10}H_{16}O_7$ (248.09)	**3.43** (s, 3H, -OCH_3(ax)) **3.63** (ps, 1H, H-5ax) **3.84** (dd, 1H, J=1.7, 12.6 Hz, H-6ax) **3.93** (dd, 1H, J=3.5, 9.7 Hz, H-3ax) **4.07** (dd, 1H, J=3.6, 9.7 Hz, H-2eq) **4.11** (dd, 1H, J=3.0, 12.6 Hz, H-6eq) **4.13** (1H, H-4eq) **4.73** (d, 1H, J=6.4 Hz, -OCH_2O-) **4.86** (d, 1H, J=5.8 Hz, -OCH_2O-) **4.91**(d, 1H, J=6.3 Hz, -OCH_2O-) **4.99** (d, 1H, J=3.6 Hz, H-1eq) **5.02** (d, 1H, J=5.8 Hz, -OCH_2O-) **5.03** (d, 1H, J=6.3 Hz, -OCH_2O-) **5.16** (d, 1H, J=6.4 Hz, -OCH_2O-).
2f	85 120	70 120	96.5 ± 1.8 (5.1, $CHCl_3$)	$C_{10}H_{16}O_7$ (248.09)	**3.31** (t, 1H, J=9.0 Hz, H-4ax) **3.40** (s, 3H, -OCH_3(ax)) **3.44** (dd, 1H, J=9.0, 10.3 Hz, H-6ax) **3.60** (dd, 1H, J=3.8, 9.0 Hz, H-2ax) **3.71** (td, 1H, J=4.8, 9.0 Hz, H-5ax) **3.93** (t, 1H, J=9.0 Hz, H-3ax) **4.13** (dd, 1H, J=4.8, 10.3 Hz, H-6eq) **4.60** (d, 1H, J=6.3 Hz, -OCH_2O-) **4.80** (d, 1H, J=3.8 Hz, H-1eq) **4.85** (d, 1H, J=5.8 Hz, -OCH_2O-) **4.89** (d, 1H, J=6.3 Hz, -OCH_2O-) **5.03** (d, 1H, J=6.3 Hz, -OCH_2O-) **5.03** (d, 1H, J=5.8 Hz, -OCH_2O-) **5.04**(d, 1H, J=6.3 Hz, -OCH_2O-).
2g	80 30	85 120	85.6 ± 1.3 (0.9, $CHCl_3$)	$C_9H_{14}O_6$ (218.08)	**3.35** (s, 3H, -OCH_3(ax)) **3.36** (t, 1H, J=9.0 Hz, H-4ax) **3.45** (dd, 1H, J=9.0, 10.3 Hz, H-6ax) **3.65** (td, 1H, J=5.0, 9.0 Hz, H-5ax) **3.90** (dd, 1H, J=1.0, 5.7 Hz, H-2eq) **4.13** (dd, 1H, J=5.0, 10.3 Hz, H-6eq) **4.25** (dd, 1H, J=5.7, 9.0 Hz, H-3ax) **4.60** (d, 1H, J=6.3 Hz,-OCH_2O-) **4.93** (s, 1H, -OCH_2(exo)O-) **4.97** (s, 1H, -OCH_2(endo)O-) **5.00** (d, 1H, J=6.3 Hz, -OCH_2O-) **5.19** (d, 1H, J=1 Hz, H-1eq).
3g	16 30	10 120	-13.6 ± 0.6 (4.4, $CHCl_3$) - 8.6 ± 0.2 (4.4,CH_3OH)	$C_{10}H_{16}O_7$ (248.09)	**3.36** (s, 3H, OCH_3(ax)) **3.57** (t, 1H, J=9.5 Hz, H-4ax) **3.72** (td, 1H, J=4.8, 9.5 Hz, H-5ax) **3.88** (dd, 1H, J=9.5, 10.2 Hz, H-6ax) **4.08** (dd, 1H, J=1.6, 3.0 Hz, H-2eq) **4.13** (dd, 1H, J=4.8, 10.2 Hz, H-6eq) **4.25** (dd, 1H, J=3.0, 9.5 Hz, H-3ax) **4.67** (d, 1H, J=6.3Hz, -OCH_2O-) **4.73** (d,1H, J=1.6 Hz, H-1ax) **4.75** (d, 1H, J=5.5 Hz, -OCH_2 O-) **4.97** (d, 1H, J=7.4 Hz, -OCH_2O-) **5.01** (d, 1H, J=5.5 Hz, -OCH_2O-) **5.06** (d, 1H, J=6.3 Hz, -OCH_2O-) **5.09** (d, 1H, J=7.4 Hz, -OCH_2O-).
2h	55 30	65 80		$C_{19}H_{28}O_2$ (212.00)	**1.00-1.55** (m, 12H, H-3, H-4, H-5) **1.69** (m, 4H, H-2ax) **1.86** (m, 4H, H-2eq) **3.53** (m, 2H, H-1) **4.73** (s, 2H, -OCH_2O-).

Table 1. ([a] Satisfactory microanalyses obtained: C: ± 0.36, H ± 0.14.)

Group 2: 1,2-Aliphatic cyclic diols.

We submitted to this reaction the quinide (**1c**) showing a *syn* diol function in 4/5 which has been transformed into the 1,3-dioxolane derivative (**2c**). The *myo*-inositol (**1d**), having one *syn* and two *anti* diol functions, has been transformed into the 1,2-dioxolane-3,4-5,6-(1,3,5-trioxaepane) derivative (**2d**). No derivative with only 1,3,5-trioxaepane function has been obtained so demonstrating the more easy formation, evidently by sterical reasons, of the 1,3-dioxolane cycle.

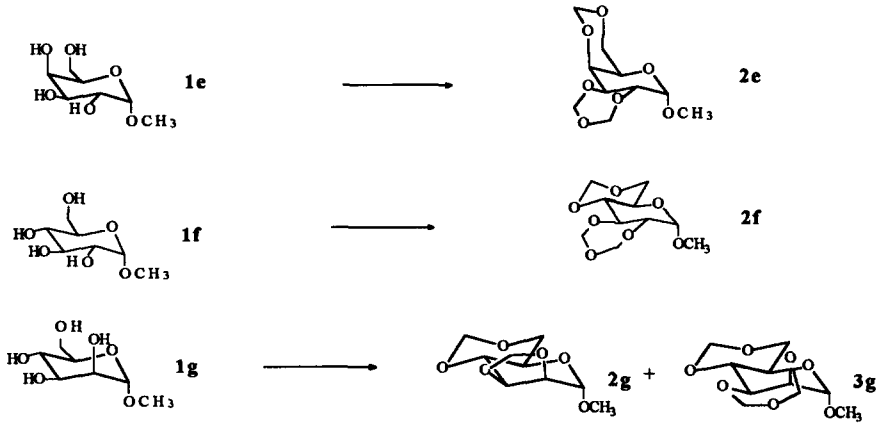


Group 3: Carbohydrates.

We used as substrates the methyl-α-D-galactopyranoside (**1e**), the methyl-α-D-glucopyranoside (**1f**) and the methyl-α-D-mannopyranoside (**1g**). The reaction on the methyl-α-D-galactopyranoside afforded a product showing a 1,3-dioxane function between the hydroxyl groups at C-6 and C-4 (axial) and a 1,3,5-trioxaepane function between the *anti* C-2 and C-3 hydroxyl groups (**2e**).

The methyl-α-D-glucopyranoside showed a similar behaviour affording a 1,3-dioxane cycle between the equatorial hydroxyl group at C-4 and the primary one at C-6, as well as the 1,3,5-trioxaepane cycle between the *anti* C-2 and C-3 hydroxyl groups (**2f**). The methyl-α-D-mannopyranoside afforded on the contrary two different compounds. The first, obtained in high yields, was the expected 2,3-dioxolane-4,6-(1,3)dioxane derivative(**2g**), while the other showed, between the *syn* hydroxyl groups at C-2 and C-3, a 1,3,5-trioxaepane function instead of the dioxolane one (**3g**).

In this case the obtaining of the dioxolane derivative has been hampered by the excessive crowding of cycles.



Group 4: Monohydric alcohols.

The cyclohexanol (**1h**) treated whit DMSO/$POCl_3$ in the above conditions gave the dicyclohexylmethylene acetal (**2h**) (55% yields). The major part of cyclohexanol was recovered unchanged, evidently, because the intermolecular reaction is slower than intramolecular one.

1h 2h

Typical experimental procedure: a solution of 1-phenyl-1,3-butanediol (*eritro*) (0.1÷1.0 g) in DMSO (1.0÷5.0 ml) was stirred under N_2 at 65°C and then added with $POCl_3$ or $SOCl_2$ (0.16÷0.8 ml).
After disappearance of the starting material (see table 1) the reaction mixture was diluted with water and extracted more times with $CHCl_3$. After the usual work-up the crude product was cromatographed on Si gel in $CHCl_3$. Yields calculated after purification: (95%).

To get some informations on the selectivity of the opening of the different cyclic acetals obtained the products **2e** and **3g** were treated in acid conditions at 50°C as after described. After ten hours the 1,3,5-trioxaepane cycle was completely hydrolysed where the 1,3-dioxane ones remained unchanged. The hydrolysis compounds **3e** and **4g** respectively were obtained with 98% yield of purified products. Therefore it is possible to deprotect regioselectively the diols involved in a 1,3,5-trioxaepane function respect to that involved in a 1,3-dioxane one, and that behaviour may cause a further use of this reaction, (see table 2).

Experimental procedure of deprotection: a solution of 4,5-(1,3-dioxane)-2,3-(1,3-dioxolane)-Me-α-D-mannopyranoside (50 mg) in acetone (2.5 ml) and 2N HCl (0.5 ml) was stirred at 50°C. After disappearance of the starting material (10 hours) the reaction mixture was neutralised with DOWEX 11. Crude product was cromatographed on Si gel in $CHCl_3$/MeOH: 95/5. Yields calculated after purification: (98%).

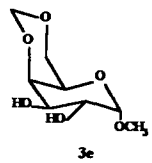
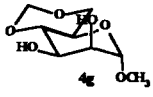
Product	Yield (%)	$t_{reac.}$ (h)	$[\alpha]_D$ c, solv	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$) δ(ppm)
 3e	98	10	150.0 ± 3.2 (0.3,CH_3OH)	$C_8H_{14}O_6$ (206.08)	**2.07** (d, 1H, J=8.6 Hz, -OH) **2.38** (d, 1H, J=7.8 Hz, OH) **3.42** (s, 3H, -OCH_3 (ax)) **3.63** (1H, H-5ax) **3.85** (2H, H-3ax, H-6ax) **4.00** (1H, H-2ax) **4.11** (1H, H-6eq) **4.72** (d, 1H, J=6.4 Hz,-OCH_2O-) **4.90** (d, 1H, J=3.5 Hz, H-1eq) **5.17** (d, 1H, J=6.4 Hz, -OCH_2O-).
 4g	98	10	26.7 ± 1.8 (0.6,CH_3OH) 18.3 ± 1.6 (0.6, $CHCl_3$)	$C_8H_{14}O_6$ (206.08)	**2.51** (ps, 2H, -OH) **3.36** (s, 3H, -OCH_3(ax)) **3.5-4.0** (5H, H-2eq, H-4ax, H-5ax, H-6eq, H-6ax) **4.12** (dd, 1H, J=3.8, 9.6 Hz, H-3ax) **4.64** (d, 1H, J=6.2 Hz,-OCH_2O-) **4.71** (d, 1H, J=1.0 Hz, H-1eq) **5.05** (d, 1H, J=6.2 Hz, -OCH_2O-).

Table 2. ([a] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.15.)

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